Editorials

Light at the End of the Tunnel?

IN AN ADDRESS BEFORE a recent meeting of the American Bar Association in San Francisco, Lee Iacocca, Chairman of the Chrysler Corporation, is reported (*San Francisco Chronicle,* Aug 11, 1987, p1,22) to have referred to litigious lawyers as "Public Enemy No. One," and he then went on to say that the number of product liability suits rose 1,000% during the period 1975 to 1985 and the amount of jury awards doubled during this time. He was further reported as stating that although cars get safer every day, automobiles account for half of all the injury suits filed and half of the awards, and that Americans are spending $30 billion a year suing each other and thus creating a climate that discourages risk taking in business, which is all important to success and even survival in a competitive world. He noted that "other countries don't spend their time looking for Mr. Deep Pockets" and called attention to the number of lawyers we have in this country by suggesting that "Japan has about as many lawyers as we have sumo wrestlers."

In medicine it is professional liability more than product liability that is the problem, but the parallels are obvious enough, and many physicians would agree that a litigious public, aided and abetted by litigious lawyers, is indeed "Public Enemy No. One," and that lawsuits and the threat of lawsuits seriously interfere with professional judgment and the taking of reasonable risks that are just as essential in patient care as they are in a competitive business such as automobile manufacturing. In both, the current epidemic of litigation has a paralyzing effect on the day to day conduct of practice or business that is not in the ultimate interest of either patients or the public. And this is not to mention the costs in dollars and human resources when these are spent in expensive, time-consuming legal confrontations that only add costly heat and friction to economic systems already under strain, again whether it be automobile manufacturing or patient care. It is all too sad, but all too true, that the most certain beneficiaries of this wave of human litigiousness are the lawyers who feed, and often feed quite handsomely, off it, as Mr Iacocca pointed out in his reported speech at the American Bar Association meeting.

For quite some time physicians and their patients have been feeling the heat and friction and, in the final analysis, bearing the costs of what has surely become excessive litigiousness in health care. As an inevitable consequence, physicians and lawyers are finding themselves in open confrontation with one another, whether in the courts or in legislative arenas, and it is worth noting that these confrontations are always on the lawyers' turf and are always conducted under rules of the game that are basically determined by lawyers.

Perhaps one can take heart, however. There may be a reason for hope. When someone of Lee Iacocca's prestige and stature in the business and industrial world calls the spade of excessive litigation the spade that it is, a new force of responsible public opinion has come upon the scene. With other nonprofessional leaders of similar prestige and stature now coming forth and speaking out in like fashion, it is just possible that we are beginning to see some light at the end of what has seemed to many physicians and many nonphysicians a very long and dismally dark tunnel.

MSMW

The Geneticist's Grail

IN A LECTURE delivered at the Western Association of Physicians meeting in Carmel, California, on February 3, 1987, Dr Ray White and co-workers reviewed and updated the current strategies used in the identification of human genetic loci. They described the recent successes in identifying the disease loci for chronic granulomatous disease, Duchenne muscular dystrophy, cystic fibrosis and retinoblastoma and referred to impending breakthroughs in a number of other diseases such as familial polyposis, ataxia telangiectasia, neurofibromatosis and other muscular dystrophies and neurologic disorders. The localization of a disease-associated gene to a region of the genome is an important first step. Once achieved, a variety of clinical applications and potential benefits can be derived from this information.

Central to the ability to map genes to a particular locus was the advent of recombinant DNA technology, which has enabled investigators to isolate genes. There are two fundamental approaches to gene isolation, depending on whether or not the protein encoded by the gene affected in a particular genetic disorder is known. When the protein has been defined, the strategy for isolating the gene is now quite straightforward. It involves the use of synthetic DNA probes constructed according to the amino acid sequence or antibodies directed against the protein of interest. The probe or antibody is then used to identify the gene that codes for the recognized protein.

A more difficult task confronts investigators who are searching for genetic loci in diseases in which the affected protein is not known and the locus on the human chromosome may or may not be defined. Linkage analysis has enabled scientists recently to map and identify DNA sequences associated with this category of disorders. Successes have included some of the most important genetic conditions that, until now, had proved largely undecipherable by classical analysis—such as neurofibromatosis, cystic fibrosis, Huntington's chorea and Duchenne muscular dystrophy. The strategy for locating these genes depends on the use of DNA polymorphisms. Within the human genome are frequent variations or polymorphisms in DNA sequences, many of which are neutral. A variety of different polymorphisms exists. One type is caused by a single nucleotide change in the DNA that either creates a restriction endonuclease cleavage site or abolishes an existing one. Digesting DNA from different persons with the appropriate enzyme generates fragments of two discrete lengths according to the presence or absence of a restriction site.

Another type of DNA fragment length variation is due to tandem repeats of short nucleotide sequences that occur in many regions throughout the human genome. The function of these tandem repeats is not known, but the number of repeats in a region differs from person to person. Therefore, digesting DNA with the appropriate enzyme generates polymorphic fragments of different lengths due to the differing number of repeats. Because of the large number of variations possible in the number of repeat sequences present, instead of a two-allele system, a highly informative multiallele system results.[1,2] Each parental chromosome can then be distinguished and used to trace the inheritance of the particular segment of the genome.

The hybridization probes used to show DNA polymorphisms can be a cloned structural gene or random unique-sequence DNA fragments isolated from a human genome. Some of the tandem repeats could also be used as probes to generate multiple alleles on multiple chromosomes.[3] The general strategy for searching for disease loci when the protein is not known is to use a series of these probes and determine which segregate together with the inheritance of a disease in a family. Once such a linked DNA marker is found, it can be assigned to a specific chromosome by hybridization analysis. The disease loci of Huntington's chorea and cystic fibrosis, for example, have been localized in this manner.

The clinical application of identifying the disease loci has been rapid. Both prenatal and presymptomatic diagnostic use of these polymorphisms is beginning to have a major impact on the practice of clinical medicine. With a DNA marker close but not right at a disease locus, how does one actually find the locus itself? This involves "walking the chromosome," that is, isolating fragments of DNA adjacent to the probe until the gene itself is reached. But how does one know which piece of DNA contains the disease locus? Several strategies are available. If the disease is caused by gene deletion, finding a DNA fragment that is deleted in the disease state indicates that one is at or very close to the disease locus. A second method is to use the adjacent DNA fragments to detect abnormal messenger RNA transcripts in the disease state. A third approach involves locating functional genes in isolated DNA. The cytosine residue of CG base pairs tends to be heavily methylated in nonfunctional DNA and remains unmethylated in functional DNA. Thus, by using restriction enzymes that can distinguish methylated from nonmethylated CG sequences, it is possible to locate DNA fragments that may contain functional genes.[4] Another characteristic of nonfunctional DNA is that the sequences tend to diverge across species, while the sequences of functional genes are usually conserved. Searching for conserved DNA sequences in DNA isolated by "walking" may also indicate the presence of functional genes. The list of disease genes that have been identified this way is small but growing.

What benefits can be derived from identifying the genetic locus for a disease? First, it provides a wealth of information about how genes function and enables us to define many mutations that may give rise to disease states. For example, we have learned that more than 50 mutations may affect β-globin gene function and result in β-thalassemia. From studying how these mutations affect gene function, we have learned why fetal hemoglobin synthesis is increased in certain types of thalassemia and why some thalassemias are more severe than others.

Apart from being intellectually satisfying, a practical application of the fundamental knowledge is better diagnostic capabilities. Whereas carrier identification of diseases such as cystic fibrosis was previously difficult, and in many cases impossible, the availability of DNA probes has overcome the obstacles. Prenatal diagnosis of many genetic conditions has become possible through the use of DNA probes. By knowing the precise mutation responsible for a disease, we are now able to design specific methods to diagnose the condition in utero. As more mutations continue to be discovered, the methods for detecting them also improve. The emergence of rapid nonradioactive techniques may help to make the DNA analysis a routine procedure.

One of the most challenging problems that DNA probes may help solve in the future relates to diseases such as heart disease and cancer that are caused by the interplay of multigenic factors. Locating these genes may help to identify factors that predispose a person to these diseases and provide methods to prevent them.

The approach we have outlined is called reverse genetics. It begins with linkage analysis to determine the disease loci, followed by determination of the gene sequence and an understanding of how the gene results in the phenotypic features of the condition. Even more important than the improved diagnostic capabilities is the potential for developing the means of treating these conditions. With this goal in mind, the isolation of genes affected in genetic disorders has already stimulated intense research efforts in replacing defective genes with normal ones. Experiments are in progress to introduce cloned genes into cells to produce missing enzymes in some enzyme deficiency states.[5] Specific recombination methods to replace a diseased gene with a normal gene have also been attempted.[6] Although these approaches are highly experimental at present, some of these therapeutic modalities may become feasible in the future.

To date, the greatest impact of modern molecular biology on the practice of clinical medicine has occurred in the field of medical genetics. An ever-increasing number of single gene disorders are now amenable to diagnosis through linkage or direct analysis of the diseased gene. Strategies using linkage analysis have led to the identification of the diseased gene in several conditions that have long baffled medical researchers. The future for diagnosing most single gene disorders through DNA analysis seems very bright, and the potential exists for effective treatment for some of them.

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Nutrition During the Continuum of Development

IN THEIR REVIEW in this issue, Kennaugh and Hay summarize information about the provision of nutrients to mammalian fetuses and the nutritional requirements of newborn human infants. By placing these respective summaries in sequence, they highlight the developmental changes in nutrient provision that occur at birth. Concurrently with the replacement of the placenta by the gut as the route for nutrient delivery and the substitution of human milk for maternal plasma as the source, both qualitative and quantitative changes in nutrition occur.

Before birth, the fetus is provided carbohydrate as glucose